AMENDMENTS TO THE DRAWINGS

The attached three (3) Replacement Sheets (1/6, 2/6 and 3/6) of drawings include lighter versions of Figures 1-5 (sheets 1/6, 2/6 and 3/6) of the originally filed application. Corresponding Annotated Sheets are not believed to be required. No new matter has been added. Entry of the attached three (3) Replacement Sheets (1/6, 2/6 and 3/6) of drawings for the originally-filed drawings sheets 1/6, 2/6 and 3/6 is requested.

REMARKS

Reconsideration is requested.

The Examiner is requested to revise the BIB DATA SHEET contained in the PTO IFW to indicate that the 35 USC § 119 requirements have been met. A certified copy of the priority document is contained in the PTO IFW, and the Examiner has acknowledged receipt of same on page 1 of the Office Action dated May 29, 2008. Alternatively, the Examiner is requested to advise the undersigned of any anything further which may be required to comply with the requirements of 35 USC § 119.

Claim 1-18 have been canceled, without prejudice. Claims 19-32 have been added. The new claims read on the elected subject matter and find support throughout the specification. No new matter has been added.

The specification has been revised to include the attached Replacement Sheets of drawings (sheets 1/6, 2/6 and 3/6) containing originally-filed Figures 1-5 in response to the Examiner's requirement for same. No new matter has been added. Entry of the attached and withdrawal of the objection to the drawings are requested.

The Title has been revised to obviate the objection to same. Withdrawal of the objection to the Title is requested.

The objection to claims 10, 11, 13, 14 and 18 is moot in view of the above. The claims are believed to read on the elected subject matter.

The Section 112, first paragraph "enablement", and first paragraph "written description", rejections of claims 10, 11, 13, 14 and 18 are moot in view of the above amendments. The claims are submitted to be supported by an enabling disclosure.

Moreover, one of ordinary skill will appreciate that the applicants were in possession of the claimed invention at the time the application was filed. Consideration of the following n this regard is requested.

The Examiner's acknowledgement that the specification is

> "enabling for a method of (1) treating cancer and (2) inhibiting endothelial cell proliferation or activation in a subject, comprising administering to a person in need of said inhibition a pharmaceutically effective amount of a protein, wherein the protein consists of the amino acid sequence SEQ ID NO:12," (see page 6 and the sentence spanning pages 7-8 of the Office Action dated May 29, 2008),

is acknowledged, with appreciation. The claims have been revised to be similar to the subject matter the Examiner has acknowledged as being supported by an enabling disclosure, without prejudice, to advance prosecution.

The claims are submitted to be supported by an enabling disclosure which adequately describes the claimed invention.

While not thought to be well founded, the Examiner's concerns regarding sequence modifications, substitutions, deletions and/or additions stated in at least pages 8-9 and 13 of the Office Action dated May 29, 2008 are believed to not be an issue with the pending claims.

The applicants submit that no more than routine experimentation would be required to make and use the claimed invention.

For completeness, the applicants note that angiogenesis is a multistep cellular and molecular mechanism implying activation, proliferation, migration and differentiation of many cell types. In particular, the neovascularization (neoangiogenesis) process

comprises an endothelial activation step (activation of endothelial cells by pro-angiogenic factors), an endothelial cell proliferation step, and an endothelial cell migration step. Considering the heterogeneity of tissues and the molecular and cellular complexities of angiogenic reactions, a single assay optimal for specifically testing all the situations of abnormal angiogenesis does not exist.

The applicants have tested the *in vivo* antiangiogenic effect of Nov and Nov C-ter with the classical general *in vivo* assay (i.e., the Corneal Micropocket (CM) assay, see Norrby et al. ("In vivo models of angiogenesis" J. Cell. Mol. Med., Vol. 10, No. 3, 2006, pp 588-612 (copy attached)) for measuring angiogenesis, known at the filing date, and evaluating the pro- or the anti- angiogenic effect of a compound.

The CM assay is an easy and assay that takes account of a characteristic property of the cornea: the complete absence of vascularization (pre-existing vessels). Therefore, the induction of neoangiogenesis in cornea is the most convincing test to demonstrate the true neovascularization (see Norrby et al. page 593, second column, and second paragraph).

Thus, when pro-angiogenic factors are injected in a pocket in the cornea, for example lipopolysaccharides LPS (see for example Kim et al, 2000 BBRC 269:401-405 (copy attached)), a neovascularization occurs rapidly to irrigate the pocket.

Therefore, if an antiangiogenic agent is added in the pocket with the angiogenesis stimulating factors, the neovascularization is reduced, or inhibited. This corresponds to the results depicted in figure 8 of the present application, wherein it is

demonstrated that Nov C-terminus fragment (SEQ ID NO 12) inhibits neovascularization induced by LPS injection.

The CM assay model is a common classical model to test the effect on endothelial activation and endothelial proliferation of a pharmaceutical agent. The use of CM assay is not restricted to assay a specific pathology such as an LPS induced corneal neovascularization, but is representative of all the pathologies involving endothelial activation and endothelial proliferation. This model mimics any neovascularization that may occur in mammals during pathologies and provides information about angiogenic properties of a compound that could modulate this "modulated"-induced angiogenesis.

Therefore, one of ordinary skill will be able to make and use the claimed invention without undue experimentation. The examples of the present application, for example, demonstrate the invention and with the advanced level of skill in the art one will require no more than reasonable experimentation to make and use the claimed invention. The specification demonstrates, for example, how to inhibit endothelial cell proliferation or endothelial cell activation, i.e., inhibiting angiogenesis.

The applicants note that Norrby et al. discloses that angiogenic assay should not induce an inflammatory response in order not to modify the neovascularization induced by the angiogenic factors (see Norrby et al. page 590, top of the second column).

To confirm the results obtained with CM test, that Nov C-ter has a general angiogenesis inhibiting effect, the applicants have also tested Nov and Nov C-ter effect on neovascularization in the Matrigel Plug (MP) assay.

As described on page 603, top of the second column, of Norrby et al., the MP assay, despite some problems of reproducibility, remains "one of the best assays for the rapid screening of potential … anti-angiogenic compounds". The applicants have injected under the skin of C57/B16 mice 300 µL of Matrigel containing 90 ng of bFGF and 90 ng of $VEGF_{165}$ as pro-angiogenic agents, supplemented with either Phosphate Buffered Saline (PBS), or 3µg of purified Nov or 3 µg Nov C-Ter. Mice were studied 7 days post injection. The Matrigel plugs were removed from each animal, photographed, and the haemoglobin content was evaluated by spectrometry at 550 nm, in each plug.

The representative haemoglobin-content results obtained with a total of 12 mice injected with PBS, Nov and Nov C-ter are represented in the attached ANNEX 1. As shown in the graph, representing means ± standard deviation of 2 experiments in which six mice were injected with PBS, Nov or Nov C-ter, the haemoglobin content in Matrigel plugs containing Nov or Nov C-ter is dramatically reduced compared to plugs containing PBS. These data demonstrate and confirm that Nov and Nov C-Ter (SEQ ID NO:12) inhibit the neovascularization induced by $VEGF_{165}$ and bFGF.

The results of the attached MP assay demonstrate and confirm that Nov and Nov C-ter inhibit *in vivo* neovascularization, i.e., neoangiogenesis, and by extension inhibit effects of bFGF and $VEGF_{165}$ on endothelial cell activation and proliferation, as described in the present specification.

One of ordinary skill in the art could make and use the claimed invention without undue experimentation.

The ordinarily skilled person will appreciate that the applicants were in possession of the claimed invention at the time the application was filed.

The claimed invention is described, for example, in the following passages: the paragraph spanning pages 3-4 and the first full paragraph of page 4 of the application; page 4, lines 7-15; page 5, line 25 through page 7, line 6; page 14, lines 14-19 and 23-24; as well as the originally-filed claims and the above-described experimental results.

The Section 112. second paragraph, rejection of claims 10, 11, 13, 14 and 18 is moot in view of the above. The pending claims are submitted to be definite.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

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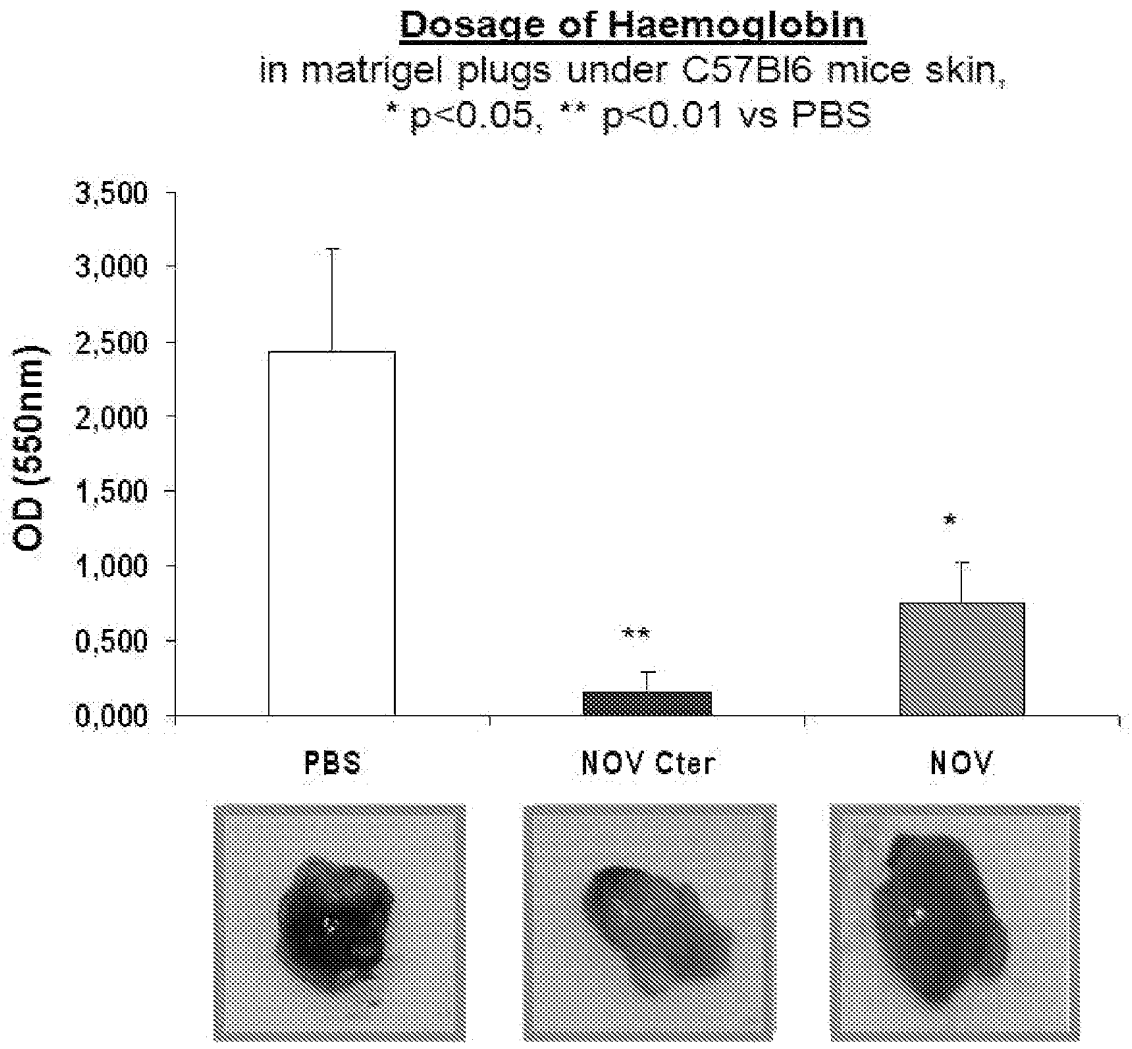
ANNEX 1


Dosage of Haemoglobin
in matrigel plugs under C57Bl6 mice skin,
* p<0.05, ** p<0.01 vs PBS
OD (550nm)
3,500
3,000
2,500
2,000
1,500
1,000
0,500
0,000
**
*
PBS
NOV Cter
NOV